BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 218 410
A3

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 86307302.9

(22) Date of filing: 23.09.86

(51) Int. Cl.⁴: A 61 K 31/44

(30) Priority: 04.10.85 GB 8524508

(43) Date of publication of application:
15.04.87 Bulletin 87/16

(88) Date of deferred publication of search report: 25.10.89

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI NL SE

(71) Applicant: BEECHAM GROUP PLC
Beecham House Great West Road
Brentford Middlesex TW8 9BD(GB)

(72) Inventor: Edwards, Peter John
7a Park Rise
Leatherhead Surrey, KT22 7HZ(GB)

(72) Inventor: Jeffryes, Carol Ann
14 Naseby Close
IsleworthMiddlesex, TW7 4JQ(GB)

(72) Inventor: Swain, Fiona Margaret
5 West Furlong
KetteringNorthamptonshire, NN15 7LF(GB)

(74) Representative: Russell, Brian John et al,
Beecham Pharmaceuticals Great Burgh Yew Tree Bottom Road
Epsom Surrey KT18 5XQ(GB)

(54) **Use of 1-hydroxy-2-pyridones in the treatment of acne.**

(57) A topical composition for application to skin affected by acne contains from 0.05 to 2% by weight of Octopirox together with a topically acceptable carrier. The composition is particularly useful for treating acne vulgaris.

EP 0 218 410 A3

Croydon Printing Company Ltd

European Patent Office

EUROPEAN SEARCH REPORT

0218410
Application Number

EP 86 30 7302

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	DE-A-3 140 954 (HOECHST) * Whole document * ---	1-7	A 61 K 31/44
X	DIALOG INFORMATION SERVICES, file 267: De Haen Drug Data, Accession no. 0141747, USAN Council: "Piroctone", & J. AM. MED. ASSOC., 1979;242:2466 ---	1-7	
X	DIALOG INFORMATION SERVICES, file 267: De Haen Drug Data, accession no. 0141749, USAN Council: "Piroctone", J. AM. MED. ASSOC., 1979;242:1912 ---	1-7	
A	EP-A-0 117 080 (UNILEVER) * Page 34, examples 22-23 * ---	1-7	
A,D	FR-A-2 191 904 (HOECHST) * Page 12, lines 1-20; page 1, line 1 - page 2, line 13 * & US-A-4 185 106 -----	1-7	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	10-08-1989	GERLI P.F.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 218 410**
A2

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 86307302.9

(22) Date of filing: 23.09.86

(51) Int. Cl.⁴: A 61 K 31/44

(30) Priority: 04.10.85 GB 8524508

(43) Date of publication of application: 15.04.87 Bulletin 87/16

(84) Designated Contracting States: AT BE CH DE FR GB IT LI NL SE

(71) Applicant: BEECHAM GROUP PLC, Beecham House Great West Road, Brentford Middlesex TW8 9BD (GB)

(72) Inventor: Edwards, Peter John, 7a Park Rise, Leatherhead Surrey, KT22 7HZ (GB)
Inventor: Jeffryes, Carol Ann, 14 Naseby Close, Isleworth§Middlesex, TW7 4JQ (GB)
Inventor: Swain, Fiona Margaret, 5 West Furlong, Kettering§Northamptonshire, NN15 7LF (GB)

(74) Representative: Russell, Brian John et al, European Patent Attorney Beecham Pharmaceuticals Great Burgh Yew Tree Bottom Road, Epsom Surrey KT18 5XQ (GB)

(54) **Use of 1-hydroxy-2-pyridones in the treatment of acne.**

(57) A topical composition for application to skin affected by acne contains from 0.05 to 2% by weight of Octopirox together with a topically acceptable carrier. The composition is particularly useful for treating acne vulgaris.

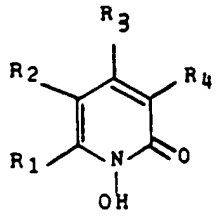
EP 0 218 410 A2

Composition

The present invention relates to a pharmaceutical composition for topical use, which contains a 1-hydroxy-2-pyridone or a salt thereof. In particular, the invention relates to a pharmaceutical composition for the treatment of acne.

US Patent No 4185106 discloses a class of 1-hydroxy-2-pyridones which are described as being useful as anti-dandruff agents. It has now surprisingly been discovered that this class of materials is useful for the treatment of acne, which is nowhere mentioned or suggested in the aforementioned US Patent.

Accordingly, the present invention provides a topical composition suitable for application to skin which is affected by acne, comprising from 0.05 to 2% by weight of a compound of formula (I).



(I)

or a topically acceptable salt thereof in which

R_1 is hydrogen, alkyl of 1 to 17 carbon atoms, alkenyl of 2 to 17 carbon atoms, cycloakyl of 5 to 8 carbon atoms, bicycloalkyl of 7 to 9 carbon atoms, cycloalkylalkyl of 1 to 4 alkyl carbon atoms, the cycloalkyl groups being optionally substituted by alkyl groups of 1 to 4 carbon atoms,aryl, aralkyl of 1 to 4 alkyl carbon atoms, arylalkenyl of 2 to 4 alkenyl carbon atoms, aryloxy-alkyl or arylthio-alkyl of 1 to 4 alkyl carbon atoms, benzhydryl, phenylsulfonylalkyl of 1 to 4 alkyl carbon atoms, furyl or furylalkenyl of 2 to 4 alkenyl carbon atoms, all the aryl groups mentioned being optionally substituted by alkyl of 1 to 4 carbon atoms, by alkoxy of 1 to 4 carbon atoms, by nitro, cyano or halogen;

R_2 is hydrogen, alkyl of 1 to 4 carbon atoms, alkenyl or alkinyl of 2 to 4 carbon atoms, halogen or benzyl;

R_3 is hydrogen, alkyl of 1 to 4 carbon atoms or phenyl; and

R_4 is hydrogen, alkyl of 1 to 4 carbon atoms, alkenyl of 2 to 4 carbon atoms, methoxymethyl, halogen or benzyl,

together with a topically acceptable carrier.

Preferred and exemplified compounds of formula (I) are those which are disclosed in the aforementioned US Patent No 4185106.

A particularly preferred compound of formula (I) is 1-hydroxy-4-methyl-6-(2,4,4-trimethyl pentyl)2(IH)-pyridone ethanolamine salt.

The preferred quantity of the compound of formula (I) or salt thereof in the composition of the invention is from 0.05 to 0.5% by weight, more preferably from 0.2 to 0.5% by weight.

In a further aspect of the invention, there is provided the use of a compound of formula (I), as hereinbefore defined, for the manufacture of a pharmaceutical composition for treating acne in humans, preferably acne in which the organism Propionibacterium acnes is implicated.

In a still further aspect of the invention, there is provided a method of treating acne in humans comprising applying a topical composition containing a compound of formula (I)or a salt thereof to the skin of a human suffering from acne.

A particularly preferred use for the composition of the invention is for the treatment of acne vulgaris, which is a polymorphic skin eruption characterised

clinically by blackheads, white heads, papules, nodules, cysts and scars occuring particularly on areas of the skin rich in sebaceous glands, such as the face, forehead and back.

The topical composition of the invention may be presented in a wide variety of different forms, for example, creams, gels, ointments, lotions,sticks, soaps (liquid or solid), bath additives, shower gels, cleansing pads, impregnated wipes, face packs, shaving foams, aftershaves, atomiser sprays and other conventional cosmetic formulations.

The major requirement in the composition of the invention is that the topically acceptable carrier (which can be any ingredient conventionally used in the abovementioned compositions) should be non-irritant to an acne sufferer.

Normally, the composition of the invention would be applied two or perhaps three times daily, in accordance with conventional application techniques for topical formulations. The dosage level of active ingredient will depend primarily on whether the composition is a 'leave on' material, such as an

ointment, or a 'rinse-off' material, such as a soap. Generally speaking, the dose for a 'rinse-off' formulation would be two or three times that of a 'leave-on' formulation.

Compositions of the invention may be produced by conventional techniques for the manufacture of pharmaceuticals or cosmetics, usually involving admixture of the various ingredients to obtain a uniform composition.

The invention is now illustrated by the following Examples:

Example 1

Gel	w/w per cent
[1]Octopirox	0.25
Menthol	10.00
DEA-oleth-3 phosphate	2.50
[2]Hydroxypropylcellulose	2.50
Amphoteric - 1	5.00
Water	39.75
Ethanol (96%)	40.00

Example 2

Cream	w/w per cent
[3]Laneth - 10	2.00
Lanolin alcohol	0.50
[4]Cetyl alcohol	5.50
[4]Polawax	6.00
[1]Myristyl myristate	2.00
[1]Octopirox	0.25
Resorcinol mono-acetate	0.2
Magnesium aluminium silicate	4.00
Methyl paraben	0.20
Sulphur	1.40
Perfume	q.s.
Water	77.95

Preparation: Dissolve the Octopirox in the propylene glycol and then add the rest of the oil phase ingredients. Add the magnesium aluminium silicate to the water at 75°C and disperse under shear again to dispense. Combine the phases and emulsify at 70°C, adding the perfume at 50°C.

[1] Trade Mark of Hoescht for 1-hydroxy-4-methyl-6-(2,4,4-trimethyl pentyl) 2(1H)-pyridone ethanolamine salt.

2 Amphoteric-1 is the CTFA adopted name for cocoamphoglycinate.

3 Laneth-10 is the CTFA adopted name for glyceryl lanolate.

4 Polawax is a Trade Mark of Croda Chemicals Ltd.

Example 3

Aerosol shaving cream

		w/w per cent
Part A	Stearic acid	4.0
	Lauric acid	2.0
	Liquid lanolin	1.0
Part B	[1]Cromeen	3.0
	Triethanolamine	2.5
	Octopirox	0.5
	Water (deionized)	87.0
	Perfume	q.s.
	Concentrate	92.0
	[2]Propellents 12/114 (40:60)	8.0

[1]Cromeen (Croda Chemicals Ltd) is a substituted alkyl amine derivative of various lanolin acids.

[2]Propellent 12 - Dichlorodifluoromethane. (B.P.).
Propellent 114- Dichlorotetrafluoromethane. (B.P.)

Example 4

Hydrocarbon-propelled aerosol shaving foam

		w/w per cent
Part A	Palmitic acid	5.0
	Lauric acid	1.0
Part B	Sodium lauryl sulphate	1.0
	Polyethylene glycol (400) monolaurate	0.5
	Polyacrylic acid (40% aq) mol. wt 100 000	1.5
	Triethanolamine	2.0
	Potassium hydroxide	0.8
	Glycerol	5.0
	Octopirox	0.5
	Water (deionized)	2.8
	Perfume	q.s.
	Concentrate	96.9
	Propellants, isobutane/propane	3.1

Preparation: Heat parts A and B separately to 75°C. Add A to B with vigorous stirring and allow to cool to 35°C, when the perfume is added. The aerosol container is charged when the concentrate has reached room temperature.

Example 5

After shave lotion	w/w per cent
Octopirox	0.25
Ethyl alcohol, specially denatured	60
Propylene glycol	3
Water, demineralised	35.75
Perfume	1

Preparation: Dissolve the perfume and propylene glycol in the alcohol and add the water slowly, stirring well to avoid locally high concentrations of water precipitating the less soluble components of the perfume. Allow the solution to stand for several hours at about 4°C, then filter.

Example 6

Bath Liquid	w/w per cent
Octopirox	2
Sodium lauryl ether sulphate (28% active)	50
Coconut diethanolamide	3
Perfume	1-2
Citric acid	q.s. to pH 7
Colour, preservative, emollients, solubilizer	q.s.
Sodium chloride	q.s. to required viscosity
Water	to 100

Example 7

Lotion	w/w Per cent
Octopirox	0.25
Alcohol	43.00
Aluminium chlorhydroxyallantoinate	0.20
Propylene glycol,	3.00
Menthol	0.05
Aluminium chlorhydrate (50%)	5.00
Hydroxypropylmethylcellulose (3%)	47.75
Mica (and) titanium dioxide	1.00
Pefume, colour, preservative	q.s.

Example 8

Stick	w/w per cent
Sodium stearate	8.00
Ethyl alcohol	74.75
Propylene glycol	10.00
Isopropyl myristate	5.00
Octopirox	0.25
Perfume	2.00

Procedure: Slurry the soap in the cold with organic solvents and Octopirox and then heat to 60° - 75°C Stir the mass while hot until clear. Add fragrance and colour as desired at 5° - 8°C above the set point of the stick. When it is uniform, pour the soap solution into moulds and allow to cool. Sodium stearate can be prepared in situ but critical control is required to avoid excess alkali or fatty acid.

Example 9	w/w per cent
Aerosol	
Octopirox	0.25
Propylene glycol	2.00
Alcohol (99% v/v)	57.25
Perfume	0.50
Propellant 12	40.00

Example 10	w/w per cent
Clear gel face mask	
Sodium magnesium sililcate	8.00
PEG - 75	1.00
Octopirox	0.20
Alcohol	5.00
Carbomer	to pH 7.5
Water	to 100
Perfume, colour, preservative	q.s.

Anti-microbial activity

To demonstrate the effectiveness of the preferred compound, Octopirox, of the composition of the present invention, the compound was subjected to in vitro evaluation by agar diffusion against P. acnes and S. aureus.

Method

Octopirox was evaluated at the 0.2%w/v level in either 10% ethanol or 10% *Tween 20.
0.1 ml of each solution was placed in a 1 cm diameter well in Brain Heart Infusion Agar (OXOID) seeded with either Propionibacterium acnes (strain 737) or Staphylococcus aureus (NCTC 6738).

*Tween is a trade mark of Atlas; Tween 20 is polyoxyethylene sorbitan monolaurate.

The plates containing Staph. aureus were incubated aerobically for 24 hours at 37°C and those seeded with P. acnes anaerobically for 48 hours at 37°C.

Results

Zone of Inhibition diameter (mm) (N=2a)

	P.acnes		S.aureus	
	10% IMS	10% Tween	10% IMS	10% Tween
No antimicrobial	NZ	NZ*	NZ	NZ
Octopirox	20.6	30	19	22.7

NZ = No zone of inhibition

* Zone of precipitation resulting from extracellular esterase activity.

Conclusion

The results demonstrate that Octopirox is effective against the organism P.acnes which is associated with the occurence of acne in humans.

Activity of Octopirox VS P. Acnes in the presence of an artificial sebum composition

Method

0.1ml of the test solutions/suspensions listed below were incorporated into 1cm wells cut into the surface of 245 x 245cm assay plates of brain heart infusion agar seeded with P.Acnes (strain 737) at a level of approx 10^6 cfu/ml. Zone of inhibition diameters were assessed after 48 hours anaerobic incubation at 37°C.

Test Agents

1. Octopirox (0.2%w/v) in 20% ethanolic solution.
2. As 1 above but also containing 10% artificial sebum.
3. Control - 20% ethanol.
4. Control - 20% ethanol + 10% artificial sebum.

Results

AGENT	mean zone diameter(mm)(n=3)	
	-sebum	+10% sebum
Octopirox (0.2%)	18.2	18.7
20% ethanol	No zone	No zone
20% ethanol + 10% Artificial sebum	No zone	No zone

Conclusion The results clearly demonstrate the ability of Octopirox to retain activity against P. Acnes in the presence of an artificial sebum composition.

The artificial sebum used in the above test method has the following composition:

Ingredient	% w/w
Triglyceride Mix (1)	36
Fatty Acid Mix (2)	24
Cholesterol	4
Lanolin	8
Squalene	12
Glycerol	8
Water	to 100%

Triglyceride Mix (1)

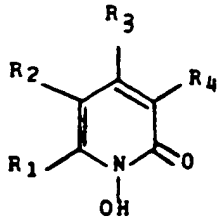
Glycerol palmitate	10 g
Glycerol oleate	10 g

Fatty Acid Mix (2)

Palmitic Acid	10 g
Oleic Acid	5 g
Myristic Acid	5 g

Claims

1. A topical composition suitable for application to skin which is affected by acne, comprising from 0.05 to 2% by weight of a compound of formula (I).



(I)

or a topically acceptable salt thereof in which

R_1 is hydrogen, alkyl of 1 to 17 carbon atoms, alkenyl of 2 to 17 carbon atoms, cycloakyl of 5 to 8 carbon atoms, bicycloalkyl of 7 to 9 carbon atoms, cycloalkylalkyl of 1 to 4 alkyl carbon atoms, the cycloalkyl groups being optionally substituted by alkyl groups of 1 to 4 carbon atoms,aryl, aralkyl of 1 to 4 alkyl carbon atoms, arylalkenyl of 2 to 4 alkenyl carbon atoms, aryloxy-alkyl or arylthio-alkyl of 1 to 4 alkyl carbon atoms, benzhydryl, phenylsulfonylalkyl of 1 to 4 alkyl carbon atoms, furyl or furylalkenyl of 2 to 4 alkenyl carbon atoms, all the aryl groups mentioned being optionally substituted by alkyl of 1 to 4 carbon atoms, by alkoxy of 1 to 4 carbon atoms, by nitro, cyano or halogen;

R_2 is hydrogen, alkyl of 1 to 4 carbon atoms, alkenyl or alkinyl of 2 to 4 carbon atoms, halogen or benzyl;

R_3 is hydrogen, alkyl of 1 to 4 carbon atoms or phenyl; and

R_4 is hydrogen, alkyl of 1 to 4 carbon atoms, alkenyl of 2 to 4 carbon atoms, methoxymethyl, halogen or benzyl,

together with a topically acceptable carrier.

2. A composition according to claim 1, in which the compound of formula (I) is 1-hydroxy-4-methyl-6-(2,4,4,-trimethyl pentyl)2(IH)-pyridone ethanolamine salt.

3. A composition according to claim 1 or 2, in which the compound of formula (I) or salt thereof is present in an amount of from 0.05 to 0.5% by weight.

4. A composition according to any one of claims 1 to 3 in the form of a cream, gel, ointment or lotion.

5. The use of a compound of formula (I) or salt thereof, as defined in claim 1, for the manufacture of a pharmaceutical composition for treating acne in humans.

6. The use according to claim 5, in which the organism implicated in acne is Propionibacterium acnes.

7. The use according to claim 5, in which the composition is for the treatment of acne vulgaris.